Redox Biology of Tuberculosis Pathogenesis

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ABSTRACT

Mycobacterium tuberculosis (Mtb) is one of the most successful human pathogens. Mtb is persistently exposed to numerous oxidoreductive stresses during its pathogenic cycle of infection and transmission. The distinctive ability of Mtb, not only to survive the redox stress manifested by the host but also to use it for synchronizing the metabolic pathways and expression of virulence factors, is central to its success as a pathogen. This review describes the paradigmatic redox and hypoxia sensors employed by Mtb to continuously monitor variations in the intracellular redox state and the surrounding microenvironment. Two component proteins, namely, DosS and DosT, are employed by Mtb to sense changes in oxygen, nitric oxide, and carbon monoxide levels, while WhiB3 and anti-sigma factor RsrA are used to monitor changes in intracellular redox state. Using these and other unidentified redox sensors, Mtb orchestrates its metabolic pathways to survive in nutrient-deficient, acidic, oxidative, nitrosative, and hypoxic environments inside granulomas or infectious lesions. A number of these metabolic pathways are unique to mycobacteria and thus represent potential drug targets. In addition, Mtb employs versatile machinery of the mycothiol and thioredoxin systems to ensure a reductive intracellular environment for optimal functioning of its proteins even upon exposure to oxidative stress. Mtb also utilizes a battery of protective enzymes, such as

ADVANCES IN MICROBIAL PHYSIOLOGY, VOL. 60
ISSN: 0065-2911
DOI: 10.1016/B978-0-12-398264-3.00004-8

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